


BMJ Open Series of virtual light therapy interventions for fatigue: a feasibility pilot study protocol for a series of personalised (N-of-1) trials

Mark Butler ¹, Stefani D'Angelo,¹ Courtney Lewis,¹ Danielle Miller,¹ Alexandra Perrin,¹ Jerry Suls,¹ Thevaa Chandereng,² Ying Kuen Cheung,² Karina W Davidson^{1,3}

To cite: Butler M, D'Angelo S, Lewis C, *et al*. Series of virtual light therapy interventions for fatigue: a feasibility pilot study protocol for a series of personalised (N-of-1) trials. *BMJ Open* 2022;**12**:e055518. doi:10.1136/bmjopen-2021-055518

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-055518>).

Received 14 July 2021
Accepted 30 June 2022



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¹Institute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA

²Mailman School of Public Health, Columbia University, New York, New York, USA

³Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Hempstead, New York, USA

Correspondence to

Dr Mark Butler;
markbutler@northwell.edu

ABSTRACT

Introduction Fatigue is one of the most commonly recorded patient symptoms that can result in deficits in aspects of psychomotor functioning, cognition, work performance and mood. Research shows that bright light and dim light therapy may be an efficacious way to reduce symptoms of fatigue. Still, the feasibility, scalability, individual treatment effects and adverse event heterogeneity of these treatments are unknown.

Methods and analysis The current study evaluates the feasibility, acceptability and effectiveness of a series of personalised (N-of-1) interventions for virtual delivery of bright light therapy and dim light therapy versus usual care treatment for fatigue in 60 participants. We hypothesise that this study will provide valuable information about implementing virtual, N-of-1 randomised controlled trials (RCTs) for fatigue. It will also offer results about determining participants' ratings of usability and satisfaction with the virtual, personalised intervention delivery system; evaluating participants' improvement of fatigue symptoms; and, in the long term, identify ways to integrate N-of-1 light therapy trials into patient care.

Ethics and dissemination This trial was approved by the Northwell Health Institutional Review Board. The trial results will be published in a peer-reviewed journal. All publications resulting from this series of personalised trials will follow the Consolidated Standards of Reporting Trials extension for N-of-1 trials CENT 2015 reporting guidelines.

Registration details This trial is registered in www.ClinicalTrials.gov (number NCT04707846).

Trial registration number NCT04707846.

INTRODUCTION

Fatigue is one of the most commonly recorded patient symptoms in conversations with primary care providers.¹ Practitioner surveys indicate that 25% of patients endorse fatigue as a complaint, while 6.5% name fatigue symptoms as their primary reason for seeking treatment.² The consequences of fatigue include deficits in aspects of psychomotor functioning (eg, attention and vigilance), cognition (eg, memory and

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This trial provides a virtual, personalised intervention delivering bright light and dim light therapy for fatigue.
- ⇒ This trial will ask participants to evaluate usability and satisfaction with the intervention and thereby provide information about the acceptability of the intervention and feasibility of its integration into patient care.
- ⇒ This trial will use ecological momentary assessment, online survey measures and Fitbit Charge 3 devices to accurately assess the effect of the intervention on participant's fatigue, pain, stress, confidence, concentration, mood, activity and sleep in real-world contexts.
- ⇒ This trial's personalised (N-of-1) design allows for examination of heterogeneity of intervention effects.
- ⇒ This study will enrol 60 participants and assess them for a duration of 14 weeks.

reasoning), work performance and mood.^{3–5} In the general population, fatigue is associated with increased workplace accidents, highway mortality and reduced quality of life.^{6–9} Despite the high prevalence of fatigue symptoms, therapies are without clear guidelines by which to address these symptoms.

Fatigue may stem from many causes, one of which is disruption of circadian rhythms that control the sleep–wakefulness cycle.^{10–12} Reviews indicate that bright-light therapy can reduce fatigue via two circadian rhythm mechanisms: (a) light influences the suprachiasmatic nucleus (SCN), a region in the hypothalamus that controls circadian rhythms; and (b) light has alerting effects, which in turn facilitate thalamic and cortical connections.^{13 14} The SCN acts as the pacemaker for circadian rhythm within the brain, with light exposure helping to trigger mammalian sleep and wake states.^{13 15} Studies

in mammals have found that blue light exposure can alter the functioning of the circadian clock in the SCN, linking the exposure to increased alertness and wakefulness.¹⁶ In addition, light exposure has also been shown to activate the posterior thalamus, a region associated with alertness, and in the parietal, temporal and occipital lobes of the cortex.^{14 17} Intervention trials¹⁸ have also found that brief morning exposure to bright light (BL) improves subjective symptoms and performance in nurses with rapidly rotating shifts—individuals who are particularly at risk for circadian rhythm disruption.¹⁹

Based on the effect of light on the circadian rhythm, bright-light therapy has emerged as a potentially viable treatment for fatigue but has been found to have small to moderate effects.^{20–22} A meta-analysis examining 53 studies of BL treatment found that BL exposure was associated with reduced general levels of sleep problems, circadian rhythm sleep disorders, insomnia and sleep disruptions related to Alzheimer's disease.²⁰ However, this same meta-analysis showed heterogeneity of treatment effects for light therapy that potential moderator variables (such as sex, age and study design) have not explained.²⁰ Further complicating findings, dim light (DL) has also demonstrated varying levels of effectiveness on fatigue and called into question the use of solely BL therapy.²² This research indicates that, though the use of light therapy for fatigue has been studied, the utility of BL and DL therapy for individual patients is still unknown.

Personalised (N-of-1) trials are a patient-centred research approach that can provide important clinical information for patients in selecting which treatments work best for them. In a personalised trial design, individual patients are assessed using multiple crossover trials with objective data collected continuously throughout the trial with alternating time periods of treatment, alternative treatment and placebo therapies in randomised blocks.^{23 24} Personalised trials are specifically designed to help patients make healthcare decisions informed by high-integrity, evidence-based information uniquely relevant to the outcomes and values important to them.²⁵ Prior series of personalised trials led participants to changes in treatment, cessation of treatment or confirmation of the initial treatment.^{23–27} Despite the utility of personalised trials at the patient level, N-of-1 personalised designs are seldom used in clinical practice.^{23 28–30} In surveys that examined attitudes about personalised trials, respondents concluded that the potential benefits of personalised designs did not match the cost and effort required for implementation.^{23 28 30} However, personalised trials have often been initiated with clinicians serving as the target audience for results rather than patients.³⁰ If personalised N-of-1 trials are conducted with patients as the target audience and conducted in a cost-effective manner, this will increase the use of personalised designs to determine individual-level patient benefits and harms.

Most studies on the effects of BL therapy on fatigue have involved between-subject RCTs.^{20–22} Although such trials often report significant benefits on average, not all

individuals show substantial gains and may instead experience modest or no effects. The heterogeneity of effects is of concern and fails to confirm a common assumption of clinical triallists that between-subject treatment change will be roughly equivalent to within-subject treatment change.³¹ A personalised trial involving a single, within-subject experimental approach can evaluate the optimum treatment for a single patient. Since each patient serves as their own control, these crossover trials eliminate confounding by covariates. Given the previously shown heterogeneity in studies examining the effects of light therapy on fatigue, the N-of-1 personalised design is ideal for assessing the effects of light therapy on participants suffering from fatigue. Furthermore, this intervention is designed for a single patient and so estimates the fatigue improvements and side effects quantitatively for that single patient. This allows a clinician and patient to determine if a treatment has net benefit for that patient, rather than trying to guess the benefit for the patient based on data obtained from other trial participants and averaged and summarised in published articles.

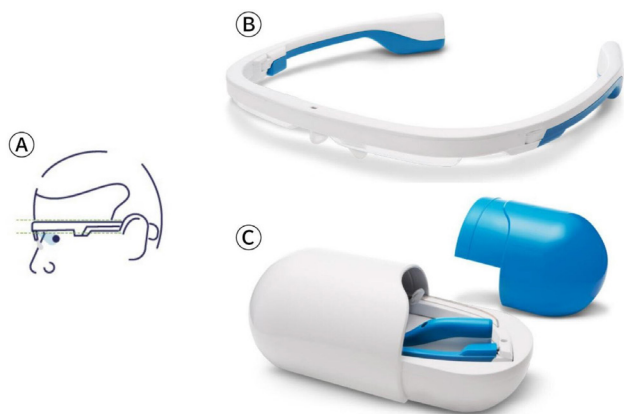
The current study evaluates the feasibility, acceptability and effectiveness of a series of N-of-1 interventions for virtual delivery of BL therapy, DL therapy or usual care treatment for fatigue symptoms in 60 participants. By using new wearable technologies (such as Fitbit devices) and commercially available light therapy devices (such as AYO), the current study allows for continuous data collection and virtually conducted assessment. Furthermore, virtual delivery of the intervention allows each participant to receive treatment and be assessed for fatigue in their own home. Results from this study will determine whether virtual delivery of these interventions is feasible and acceptable for participants with fatigue and allow clinicians to identify for which patients virtual delivery of light therapy can effectively treat fatigue.

METHODS

Study design

The study is a series of 60 randomised N-of-1 trials examining the effects of BL and DL versus usual care on fatigue. The intervention will be delivered virtually to participants across the USA over 14 weeks. Participants will be provided with a Fitbit Charge 3 device and two AYO light therapy devices.

Worn similarly to glasses, AYO is a commercially available wearable light therapy device that uses blue (470 nm±2 nm wavelength) light of±100 Lux and irradiance of±250 µW/cm².³² A device emitting a blue light wavelength of 470 nm was preferable to similar devices, as those emitting this wavelength may offer increased ocular protection.³³ AYO rests above the eyes and emits light down into the user's eyes via four light-emitting diodes. [Figure 1](#) displays the proper position for wearing the AYO device. Using a short 'lens', the AYO diffuses light and thereby reduces glare and increases the comfort of device use. Unlike desktop or free-standing light therapy, the



A – Proper position for wearing the AYO Light Therapy Glasses
 B – The AYO Light Therapy Glasses
 C – AYO Light Therapy Glasses in charging case

Figure 1 The AYO light therapy glasses: proper use and charging.

AYO allows users to continue with everyday tasks while completing their light therapy sessions. AYO devices were specifically chosen to address safety concerns and concerns raised by participants during alpha-piloting of the light-therapy-for-fatigue study. AYO light therapy glasses can easily turn on/off and have a charging case that connects directly to a power source. In addition, the diffused LED light was more comfortable on the eyes than alternative wearables and adheres to safety recommendations for luminosity.³⁴ Smartphone activation allows participants to start their light therapy session from their phone, and automatic shut-off eliminates the need to set a separate timer to end the session. Furthermore, Bluetooth capability allows research staff to remotely monitor sessions to ensure participants' safety and proper adherence to study protocol.

The first 2 weeks of the study will be a baseline assessment period. Participants will not be able to use any light therapy during this time. During baseline assessment, each study participant will be asked to both engage in their usual methods of managing fatigue symptoms and wear their Fitbit device at all times, including during sleep. Participants will also be asked to rate an ecological momentary assessment (EMA) of their fatigue symptoms, pain, concentration, stress, mood and confidence three times daily via text message. Each evening, participants will answer a survey questionnaire assessing their symptoms of fatigue from that day. Each weekend, participants will complete a longer survey measure asking them to reflect on their fatigue symptoms over the week. Participants will be encouraged to wear their Fitbit devices day and night and will be asked to sync their device with the Fitbit application on their phone at least every 2 days and charge their Fitbit device at least every 4 days.

After successfully completing the baseline period, participants will be randomised into two arms with six 2-week treatment blocks of BL AYO therapy, DL AYO therapy or usual care. During BL and DL intervention

periods, participants will be discouraged from receiving additional light therapy or fatigue treatments outside those provided during the study. Only the commercial 'high' light setting on the AYO device will be used for BL periods within this study. During DL periods, an additional non-commercial version of the AYO—using 1% of regular intensity, less than 2lux—will be used. During usual care periods, no treatment will be provided to participants, and they will be discouraged from engaging in light therapy treatment on their own. At the end of the 14 weeks, each participant will be provided with a satisfaction survey and report containing their analysed data. This report will be sent within 3 months of study completion. After the satisfaction survey is completed, study coordinators will reach out to each participant to interview them about their experience with the personalised trial. Study recruitment began in December 2020, and the study completion is anticipated to occur in December 2021. Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used in this protocol.³⁵

Study population

Participants in the current study, including employees within the Northwell Health system, will be volunteer subjects from across the USA. Comprised of approximately 77 000 employees, Northwell Health offers a large pool of potential participants affiliated with the organisation.³⁶ To expand beyond the Northwell Health system, recruitment will also use the US's internet and social media users. All participants in the study will self-identify as having a minimum threshold of fatigue. Due to the high prevalence of fatigue² and the potential reach of our outreach methods (69% of US adults report ever using Facebook, 18% report using Reddit and 93% report using the internet),³⁷ the potential study population is anticipated to be quite sizeable. After consultation from an ophthalmologist expert, the study will exclude participants with a family history of Stargardt's disease and exclude those with diabetes for eye vision safety reasons.

Inclusion criteria

Participants must meet the following criteria to be included in the study:

- ▶ Are 18–59 years of age.
- ▶ Are fluent in English.
- ▶ Have self-reported fatigue scores of ≥ 12 on a modified Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a scale.
- ▶ Are able to participate in blue light therapy.
- ▶ Possess a smartphone capable of receiving text messages.
- ▶ Possess an email account that can be regularly accessed.
- ▶ Live in the USA.

Exclusion criteria

Persons who meet the following criteria will be excluded:

- ▶ Are <18 years old or >60 years old.
- ▶ Are pregnant.
- ▶ Have had previous diagnosis of eye disease, such as cataracts, glaucoma, macular degeneration, Stargardt or family history of Stargardt, retinitis or retinopathy or other retinal disorders.
- ▶ Have had previous diagnosis of diabetes.
- ▶ Have had previous eye surgery.
- ▶ Have sensitivity to light or use of medication causing sensitivity to light.
- ▶ Have epilepsy or a history of seizures.
- ▶ Participate in shift work (evening/night shifts, early morning shifts, rotating shifts, etc).
- ▶ Have had a previous diagnosis of a serious mental health condition or psychiatric disorder that could be exacerbated by exposure to light therapy or that would compromise their ability to engage with full consent in this trial or adhere to the protocol.

Recruitment

Potential participants will primarily be recruited via advertising and posting across Facebook, Instagram, Google and Reddit. Several iterations of Facebook and Google advertising campaigns will be used to identify the best methods and target different subpopulations (namely by gender or US state of residence). Various formats of recruitment information (including videos, images and text posts) will be posted in online interest group communities on Facebook and Reddit. In addition to word of mouth, recruitment methods will also include emails sent out to all Northwell Health employees and individuals who previously expressed interest in Personalized Trials and the Northwell Health Clinical Trials Listing. Interested persons will be directed to an online information screen with details about the pilot study and asked to complete an initial screening measure containing questions regarding study inclusion and exclusion criteria. This information will be reviewed by study staff to determine participant eligibility prior to consent. If a potential participant is deemed ineligible or is waitlisted due to high demand, study staff will reach out to the participant to notify them within two business days. If the participant is deemed eligible, they will be asked to select times when they are available for a 30 min educational phone call with a study staff member. A study staff member will confirm the scheduled time with the participant within two business days. After the phone call, the study staff will send the eligible participant a message containing the electronic consent form and additional information.

Consent

Persons who are eligible to participate after the screening and educational phone call will receive a message from study staff with a link to access an electronic copy of the consent form and a short video explaining key details of the study protocol and consent form. A four-question screening measure will assess participant understanding of the protocol and consent process. Consent will be

obtained electronically, and a copy of the consent will be mailed to the participant and the study instructions and devices. Signed consent forms will be stored electronically on a Health Insurance Portability and Accountability Act (HIPAA) compliant, Northwell Health approved shared drive accessible only to the IRB-approved study staff. An example consent form can be found in appendix 1—sample patient consent.

Potential participants will have the opportunity to choose from within a provided list of start dates during their enrolment process. No more than 20 potential participants will begin their baseline period on the same day. Enrolment will be ongoing until up to 60 participants have been randomised after baseline.

Assignment of interventions

Of those participants who are enrolled in the study, approximately 30 will be randomised by the study statistician to receive the protocol in the following order of balanced 2-week treatment periods: BL, DL, usual care, usual care, DL and BL. The other participants will be randomised in the following order of 2-week treatment periods: usual care, DL, BL, BL, DL and usual care. In each treatment arm, participants alternate between BL, DL and usual care periods. Randomisation of participants to one of the two treatment orders will be conducted in six blocks using a readily accessible randomisation website.³⁸ This randomisation to treatment order can be viewed in the participant timeline in [figure 2](#).

Interventions

Once a participant successfully completes baseline data collection and is found to meet all eligibility criteria, that participant will be randomised into the study and will be mailed two AYO light therapy glasses. One pair of glasses will be labelled 'Bright', indicating it has been hard-coded to emit the BL therapy treatment (blue light with 470nm±2 nm wavelength, ±100Lux, and irradiance of±250 µW/cm²). The other pair of glasses will be labelled as 'Dim', indicating it has been hard-coded to emit the DL therapy treatment (1% regular intensity; less than 2lux.). Participants are not blind to treatment condition during their 2-week treatment periods. Participants will also receive a treatment schedule indicating when they are to use BL glasses, when they are to use DL glasses and when they are to avoid light therapy treatments. Participants will be instructed to download a unique research study application that will initiate light therapy sessions at a predetermined session length of 30 min. During intervention weeks and within an hour of their self-reported wake time, participants will receive morning text message reminders instructing them to complete a 30 min session of either BL or DL each day depending on where they are in the protocol. During usual-care treatment periods, participants will be asked to refrain from participating in any light therapy and instead manage their fatigue using the methods they usually would. During all treatment

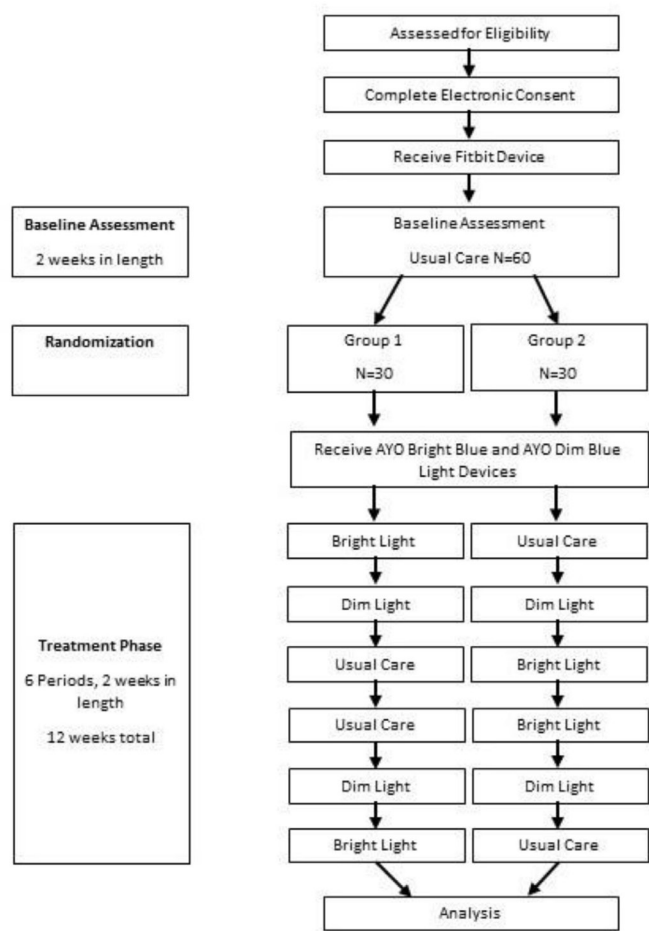


Figure 2 Participant timeline.

periods, participants will be asked to wear the Fitbit device 24 hours a day and answer four survey measures daily.

Participant timeline

Figure 2 illustrates the participant timeline.

Adherence

Participant adherence to the protocol will be assessed during the first 14 days of the baseline assessment period. During baseline assessment, study staff will review participant adherence to wearing their Fitbit, EMA measure completion and survey responses. During the 14 days of the baseline period, participants who do not achieve a minimum of 80% adherence to Fitbit wear and study measures will be withdrawn from the study. Participants maintaining 80% adherence or greater will finish out the baseline period and will be eligible to be randomised to the treatment phase of the design. Several methods will be employed to encourage adherence throughout the study. Participants will have short education videos available to them, be provided with protocol reminders via text message and be encouraged to contact study staff with concerns by phone, email or secure portal message. Participants wearing the Fitbit for more than 12 hours per day and during sleep will be defined as adherent, as

will those who respond to 80% of the EMA and survey measures.

OUTCOMES

Primary outcome

In this study, the System Usability Scale (SUS) will be used to assess the primary outcome of this design, feasibility of the intervention. The primary outcome of the current study will be the mean usability score as measured using the SUS.³⁹ This scale is a validated 10-item questionnaire that asks users to score each item on a Likert scale from strongly disagree (0) to strongly agree (4). Individual item scores are multiplied by 2.5 and summed to generate a total score ranging from 0 to 100, with higher scores indicating a greater level of usability. This measure has been used and validated in multiple contexts.^{40 41}

Secondary outcomes

Secondary outcomes in the current study will include self-reported daily fatigue, self-reported weekly fatigue, EMA self-reported fatigue ratings, EMA self-reported pain ratings, participant satisfaction, EMA self-reported concentration ratings, EMA self-reported stress ratings, EMA self-reported mood ratings, EMA self-reported confidence ratings, Fitbit device – recorded daily steps and Fitbit device – recorded nightly sleep duration. We will also measure participant adherence to survey measures, EMA assessment measures, the Fitbit device and adherence to both BL and DL therapy. Finally, potential side effects during the BL and DL therapy phases will be assessed daily.

The PROMIS fatigue scales are used to measure daily levels of participant fatigue over the past 24 hours (PROMIS Item Bank V.1.0 Fatigue 7b Daily) and weekly levels of participant fatigue over the past 7 days (PROMIS Item Bank V.1.0 Fatigue 8a). All items are rated on a scale of 1–5, with higher scores indicating higher fatigue levels. PROMIS fatigue measures are collected every evening and on the weekends, and EMAs are collected daily via surveys using the N1Thrive platform, a Northwell Health approved and HIPAA-compliant system used for patient engagement and collecting and storing research data. An N1Thrive workflow was constructed for this study to include automated messaging pathways delivered via text message directly to the participant's smartphone. For both PROMIS scales, scores will be converted to T-scores using methods from the PROMIS scoring manual based on item response theory. These will allow scores to be compared with previously established population norms. With an SD of 10, a T-score of 50 is the average for the US general population.⁴² A higher T-score represents higher levels of fatigue. The reliability and validity of the PROMIS fatigue scales have been well supported.⁴³ In the current study, the effect of BL and DL on the PROMIS fatigue scales (relative to usual care) will be used to determine the effectiveness of each intervention.

Daily self-reported fatigue, pain, concentration, stress, mood and confidence ratings will be assessed via EMA using a measure adapted from the Numeric Pain Rating Scale.⁴⁴ These assessment measures are single-item assessments administered three times daily via text message asking participants to rate their fatigue, pain, concentration, stress, mood and confidence in the current moment on a scale of 0–10. The timing of the text messages will be randomised between a participant's self-reported wake and sleep times. For fatigue, the text stated 'I feel fatigued' and ratings of 0 indicate no feeling of fatigue while scores of 1–3, 4–6, 7–9 and 10, respectively, indicate a little, some, significant and extreme feeling of fatigue. Interpretations of scores remain the same for pain, concentration, stress and confidence. For mood, ratings of 0 indicate poor mood with scores of 1–3, 4–6, 7–9 and 10, respectively, indicating a fair, good, very good and excellent mood. As with the PROMIS fatigue scales, changes in the EMA measures will be examined to determine the effectiveness of each intervention.

Measures of participant satisfaction will be used to determine the acceptability of the trial.

Patient satisfaction with the trial will be assessed using a satisfaction survey administered on completion of the treatment. The survey will assess participant satisfaction with elements of the trial, including the onboarding process, the consenting process, the AYO device, the Fitbit device, the N-of-1 trial design, assessment measures and the participant report. Participant satisfaction with the interventions (both BL and DL therapy) will also be assessed. Participants will be asked to rate their satisfaction on a scale of 1 ('not very satisfied') to 5 ('very satisfied').

Daily steps and nightly sleep duration will be assessed using non-near field communication (non-NFC) Fitbit Charge 3 devices. Both physical activity⁴⁵ and sleep duration have been linked with fatigue, indicating these may be important secondary outcomes. During baseline assessment (2 weeks) and all treatment weeks (12 weeks), participants will be asked to continue wearing their Fitbit device each day and night (for a total of 14 weeks, overall). All enrolled participants will be provided with a Fitbit study account that the research team has created with no identifying information. A file linking the Fitbit identifier to the study participant will be housed in a Northwell-approved drive to store protected health information. It will be accessible solely to members of the study team listed in the IRB application. Participant Fitbit data will be retrieved using Fitabase, a secure online portal. Participants' study accounts will then be linked to an identification number in the Fitabase system. No identifying information will be stored in the Fitabase dataset, and Fitabase will stop tracking participant data at the end of the trial. As an added security measure, participants will be instructed to remove the Fitbit study account from their smartphone device to keep the Fitbit.

ANALYSIS

Sample size calculation

The sample size of 60 participants was chosen to ensure a sufficient number of participants to obtain a preliminary assessment of the feasibility of this series of N-of-1 trials of BL and DL therapy for fatigue. In the current study, feasibility is determined by participant scores on the SUS. The numbers of assessment measures and treatment repetitions per trial were based on expert recommendations by a statistician and their estimations about the maximal duration of the trial to maintain patient engagement. The primary endpoint is trial completion in the first 3 months. We aim to demonstrate a trial completion rate greater than 50% in randomised participants. With $n=60$ and use of a 1-sample binomial test at 2.5% significance 1-sided, we will have approximately 90% power if the true completion rate is 70%. With 60 randomised participants, expecting a trial completion rate of 70%, we anticipate SUS data are available in about 42 participants, thus giving an SE no greater than 8% in estimating the rate of $SUS \geq 85$, an exceptional level of usability.⁴⁶ The SE will be the largest when the trial completion rate is at 50%. Data will be reported transparently so that individual-level heterogeneity can be assessed.⁴⁷

Primary analysis

The primary analysis will examine the feasibility of the trial measured by participant scores on the SUS. Ratings from all enrolled participants ($n=60$) on the SUS will be summarised via descriptive statistics including mean, median, SD and IQR. We will also visualise the distribution using histogram. The SUS data will be compared with established usability standards in the SUS literature to determine the relative usability of the intervention protocol. If scores on the SUS are greater or equal to 70, defined as an acceptable rating,⁴⁶ the current intervention will be judged to be feasible. To determine whether SUS ratings differ by participant characteristics, we will examine mean SUS ratings by age, sex, race and ethnicity.

Secondary analyses

Means and SDs for PROMIS daily fatigue scores, PROMIS weekly fatigue scores, self-reported EMA fatigue scores, self-reported EMA pain scores, self-reported EMA concentration scores, self-reported EMA stress scores, self-reported EMA mood scores, self-reported EMA confidence scores, Fitbit-assessed daily steps and Fitbit-assessed nightly sleep will be reported for the baseline assessment period (2 weeks) and each treatment period (six blocks of 2 weeks) and depicted graphically. Means and SDs for patient satisfaction with the trial will be calculated and reported. Higher average scores will be interpreted as higher levels of satisfaction with the trial overall and specific trial elements. We will also calculate mean and SD values for each secondary outcome across treatment periods for BL, DL and usual care. For example, we will sum all outcome measures for both 2-week massage treatment periods to derive an overall mean value for BL.

(The same process will be followed for DL and usual-care periods.) We will then compare overall means of secondary outcomes for BL, DL and usual care periods with baseline means using paired-sample t-tests.

Finally, the effects of each treatment on daily fatigue, weekly fatigue and self-reported EMA fatigue will be assessed using generalised linear mixed models with an autoregressive (AR¹) model that accounts for possible autocorrelation and linear trends between fatigue ratings across time. We will consider ‘week’ as a linear term and a factor in the mixed model to explore the non-linear time effects of each treatment. More specifically, to determine whether BL therapy or DL therapy was superior to usual care and the other light therapy for reducing fatigue among individual patients, treatment effects will be assessed using an AR model that includes the type of light therapy as the main exposure, adjusted for time (eg, days since enrolment) linearly as a covariate and accounted for autocorrelations of the order 1.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Pilot data with participants was used to help determine which light therapy device to select for the current trial. We did not directly involve participants in any other elements of the design or conduct of this trial.

DATA MONITORING

A Data and Safety Monitoring Board (DSMB) will be assigned to periodically review and evaluate project data for participant safety, scientific integrity and the trial’s progress. The DSMB will have four members from different disciplines with varying areas of expertise, such as biostatistics and behavioural medicine. The DSMB will review data for accuracy, completeness and timeliness of submission. DSMB reviews will examine for evidence of potential harms, including adverse treatment events and loss of confidentiality. Based on the data reviewed, the DSMB will be responsible for making recommendations regarding the continuation, modification and termination of the project in reports provided to the study’s principal investigator (PI). The study team will provide the DSMB with access to study data for monitoring and regulatory inspection.

HARMS

Treatment adverse events

Bright blue light therapy, which poses a low risk of physical harm to participants, is a typical treatment for symptoms of fatigue. It has been associated with several transient side effects, including jumpiness/jitteriness, headache and nausea, and mania has been infrequently observed in patients with bipolar disorder. These side effects have been observed to resolve quickly after the cessation of light therapy.

Study exclusion criteria were designed to prevent participants at greater risk of harm from participating in the study, such as found for participants with certain mental disorders or vision disorders. Light therapy protocol adherence is monitored throughout the trial, and participant re-education is conducted as needed. Participants are asked daily to report to the study team any side effects they experience that may be due to light therapy each intervention day of the study via the daily evening survey. Participants are informed that they can discontinue blue light therapy at any point during the trial.

Loss of confidentiality or privacy

One potential risk of participating in this study is loss of confidentiality or privacy. All identifying information will be stored in a secure, password-protected, Northwell Health approved, HIPAA-compliant database. Neither personal nor identifying information will be stored on any of the study devices used in the study. Furthermore, identifying information will be destroyed once a participant completes their study involvement. All research team members with access to identifiable and deidentified data will be trained and included on the IRB submission for approval. Regular meetings will occur with the PI and other study team members to ensure protocol adherence and data accuracy. The participant will be made aware of all data collected and the companies/technology employed to collect the data via the consent process.

Costs

This research study is funded by the National Institutes for Health (R01LM012836). All study-related equipment, devices, procedures and BL and DL treatments will be provided to participants at no cost. Participant insurance will not be billed. This study uses text messaging to deliver notifications, reminders and study questionnaires. Standard message and data rates from the participant’s wireless carrier may apply to the study participant. Study participants will not be compensated for any costs related to data usage or sending or receiving text messages by the study or by members of the study team.

COMPENSATION

After completing all components of the study (ie, submission of a satisfaction survey and completion of a follow-up interview), study participants will be mailed a \$100 payment card (Clincard). Additionally, to thank study participants for their participation, we will let them keep their Fitbit Charge 3 (a value of \$120.00) and 1 AYO light therapy device (a value of \$299.00).

ETHICS

All amendments to the protocol will be submitted to the ethics committee and Northwell Health IRB for approval.

DISSEMINATION

The trial results will be published in a peer-reviewed journal. All publications resulting from this series of personalised trials will follow the CONSORT extension for N-of-1 trials CENT 2015 reporting guidelines.⁴⁸ Trial results will be reported to study collaborators and participants following study completion.

Acknowledgements We are grateful for the contributions and support of the Northwell Health System and AYO by Novalogy for providing the investigators with the support and tools for the development and implementation of this trial.

Contributors KWD, SD and YC contributed to the development of the trial idea. KWD, SD, CL, DM, AP and YKC contributed to development of the trial protocol. MB, SD, JS, CL, DM, AP and KWD drafted the manuscript, and all authors contributed to its revision and gave final approval. YKC and TC provided statistical expertise.

Funding This work was supported by the National Library of Medicine of the National Institutes of Health (grant number R01LM012836).

Disclaimer The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and do not represent the views of the National Institutes of Health, the US Department of Health and Human Services or any other government entity. KWD is a member of the US Preventive Services Task Force (USPSTF). This article does not represent the views and policies of the USPSTF.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Northwell Health Human Research Protection Program Approval # 20-0835. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement As this is a protocol, no data is collected and available.

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ORCID iD

Mark Butler <http://orcid.org/0000-0003-4359-2897>

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